REMARKS

Claims 1-8 and 48 are pending. In the instant amendments, claims 49-89 drawn to non-elected subject matter have been canceled without prejudice as explained below. Claims 1, 3, 5-6, 8 and 48 have been amended. New claims 90-106 have been added. Upon entry of the claim amendments, claims 1-8, 48 and 90-106 will be pending and under consideration.

I. Amendment to the Claims

Claims 1 and 48 have been amended to recite pharmaceutically acceptable salts of the compound of Formula (I). Support for this amendment is found, for example, in paragraph [0039] of the specification.

Claims 3, 5-6 and 8 have been amended to delete the trade names of the therapeutic agents listed therein.

Claim 8 has also been amended to delete "and their active metabolites."

Claims 49-89, directed to non-elected subject matter, have been canceled without prejudice to Applicants' right to prosecute the canceled subject matter in one or more continuation, continuation-in-part, or divisional applications.

New claims 90 and 104 recite, *inter alia*, the free base of the compound of formula (I). Support for these claims is found, for example, in original claim 1 and paragraph [0020] of the specification.

New claims 91-92 and 105-106 recite, *inter alia*, hydrochloride or tartrate salts of the compound of formula (I). Support for these claims is found, for example, in paragraph [0039] of the specification.

New claim 93 recites the composition of claim 1, wherein the composition in a single unit dosage form. Support for this claim is found, for example, in paragraphs [0091] to [0093] of the specification.

New claims 94-102 recite oral dosage forms of compositions comprising a compound of Formula (I). Support for these claims is found, for example, in paragraph [0093] of the specification.

New claims 103 recites the compound of claim 48 in solid form. Support for this claim is found, for example, at page 12, paragraph [0039] of the specification.

These amendments are supported by the claims and specification as originally filed. No new matter is added by the amendments. Entry of the above amendments is respectfully requested.

II. Rejection under 35 U.S.C. § 102(b)

Claim 48 stands rejected under 35 U.S.C. § 102(b) as being anticipated by *R&D Focus Drug News*, November 12, 2001 ("*Drug News 2001*") (final Office Action, page 2).[1] Applicants respectfully disagree.

To establish anticipation under 35 U.S.C. § 102(b), the Examiner must demonstrate that each and every limitation of a claim is disclosed in the cited reference, either expressly or inherently. *See Transclean Corp. v. Bridgewood Services, Inc.*, 290 F.3d 1364, 1370 (Fed. Cir. 2002); *see also* MPEP § 2131. Claim 48 is not anticipated by *Drug News 2001* because it does not disclose the chemical structure of the compound of Formula (I) of claim 48.[2]

The Examiner alleges that *Drug News 2001* discloses that the compound of claim 48, ACP-103, is a selective 5-HT_{2A} inverse agonist with desirable pharmacological properties. (final Office Action, page 2). *Drug News 2001* does not disclose the chemical structure of the compound of Formula (I) of claim 48, nor does it provide any information about the structure of the compound (again, a copy is provided in the enclosed Information Disclosure Statement). Further, the Examiner has not demonstrated that, based upon the name "ACP-103" alone, one of ordinary skill in the art would have been able to determine the chemical structure of the compound prior to the relevant filing date. Because the Examiner has not and cannot demonstrate that *Drug News 2001* discloses each and every limitation of claim 48, the claim is not anticipated by this reference. *See Transclean*, 290 F.3d at 1370. Thus, Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) be withdrawn.

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[1] The Examiner has provided only a computerized print-out of the text of this article available on Dialog®. Attorneys for the Applicants provide, for completeness of the record and consideration by the Examiner, a copy of the published article (C27 of the enclosed Information Disclosure Statement).

[2] Although the Dialog® abstract of *Drug News 2001* recites the name "pimavanserin," Applicants point out that, in addition to the lack of a chemical structure, the name "pimavanserin" is not found in the published article.

Claim 48 stands rejected under 35 U.S.C. § 102(b) as being anticipated by *R&D Focus Drug News*, January 24, 2000 ("*Drug News 2000*") (final Office Action, page 3). Applicants respectfully disagree.

Drug News 2000 does not disclose the chemical structure of the compound of Formula (I) of claim 48, nor does it provide any information about the structure of the compound. A copy of the published article of *Drug News 2000* is provided in the enclosed Information Disclosure Statement. Indeed, *Drug News 2000* does not mention ACP-103 at all.[3] Furthermore, the Examiner has not demonstrated that, based on the name "ACP-103" alone, one of ordinary skill in the art would have been able to determine the chemical structure of the compound at the time of the invention. Because the Examiner has not demonstrated that *Drug News 2000* discloses each and every limitation of claim 48, the claim is not anticipated by this reference. *See Transclean*, 290 F.3d at 1370. Indeed, the name "ACP-103" was not associated in the published literature with a specific compound or chemical structure prior to the effective filing date of this application. Thus, the name "ACP-103" could not render the instant claims anticipated.

Further, the Examiner alleges that "R&D Focus Drug News teaches [that] pimavanserin tartrate (ACP 103) has been identified as a lead compound within its program to develop as an antipsychotic drug." (Office Action, page 3). Applicants respectfully point out that, although the Dialog® electronic abstracts of the *Drug News* articles provided by the Examiner use the name "pimavanserin" for example in the title, the name "pimavanserin" does not appear in the actual articles themselves as published. And, even if they did, the name "pimavanserin" was not associated with a chemical structure as of the effective filing date of the instant application. Thus, Applicants respectfully request that the rejections under 35 U.S.C. § 102(b) be withdrawn.

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[3] Attorneys for the Applicants obtained a copy of the published article based upon the citation provided by the Examiner in the final Office Action. Attorneys for Applicants believe that the citation is inaccurate since the publication of *Drug News 2000* on the date provided by the Examiner does not contain an article related to ACP-103 (see C26 of the enclosed Information Disclosure Statement).

III. Rejection under 35 U.S.C. § 103(a)

A. No *prima facie* case of obviousness has been made.

Claims 1-8 stand rejected under 35 U.S.C. § 103(a) as being allegedly obvious over *Drug News 2001* in view of PCT Publication No. WO 01/66521 to Andersson *et al.* ("Andersson"), further in view of Goodman & Gilman's The Pharmacological Basis of Therapeutics, 7th ed. ("Goodman & Gilman's") (final Office Action, page 3). Applicants respectfully disagree.

Instant claims 1-8 recite, *inter alia*, compositions comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof, and compositions comprising the specific compound in combination with additional therapeutic agents. As explained above, *Drug News 2001* does not disclose or suggest the structure the compound of Formula (I). Because neither Andersson nor Goodman & Gilman's cure this defect, claims 1-8 are not obvious over the references cited by the Examiner.

In the context of claims to biologically active chemical compounds, the Federal Circuit has recently affirmed the requirement that obviousness based on structural similarity must be supported by "identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound...in a particular way to achieve the claimed compound." *Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd.*, 533 F.3d 1353, 1357 (*citing Takeda Chemical Ind., Ltd. v. Alphapharm Pty., Ltd.*, 429 F.3d 1350, 1360 (Fed. Cir. 2007) (compounds at issue not *prima facie* obvious over a compound of similar structure because the prior art provided no motivation to modify that compound to arrive at the claimed compounds) (copy attached).

In *Eisai*, a case decided on July 21, 2008, the Federal Circuit held that claims to a specific compound, rabeprazole, were not obvious over the prior art's teaching of a structurally similar compound, lansoprazole. *Eisai*, 533 F.3d at 1359. Rabeprazole and lansoprazole differ only at the 4-position, wherein rabeprazole has a 4-methoxypropoxy group and lansoprazole has a 4-trifluoroethoxy group. *Id.* at 1357. The Court held that even though the prior art taught that lansoprazole had desirable chemical and biological properties and would therefore have been considered a candidate for a lead compound, there was no motivation to modify the structure of lansoprazole in the required way to arrive at

rabeprazole. *Id.* Indeed, the Court emphasized that after the Supreme Court's decision in *KSR Int'l Co. v. Teleflex Inc.*, the prior art must provide some reason or motivation to make the necessary change in structure in order for a *prima facie* case of obviousness to be made. *Eisai,* 533 F.3d at 1359 (*citing KSR Int'l Co. v. Teleflex Inc.* 127 S.Ct. 1727, 1742 (2007) (necessary to "supply some reasons for narrowing the prior art universe to a 'finite number of identified, predictable solutions.'")[4]. Thus, the Examiner is respectfully reminded that the current law of obviousness in cases concerning structurally similar compounds "requires a showing of 'adequate support in the prior art' for the change in structure." *Takeda*, 429 F.3d at 1356 (*quoting In re Grabiak*, 769 F.2d at 729).

The instant claims are not obvious because the Examiner has not shown adequate support for the change in structure required to arrive at the specific compound of the instant claims from the teachings of *Drug News 2001*, Andersson and Goodman & Gilman's. As discussed above, *Drug News 2001* merely states that a compound designated "ACP-103," the structure of which is not disclosed, is a 5-HT_{2A} inverse agonist with desirable pharmacological properties. Indeed, no structural information about the compound is provided by *Drug News 2001*, and one of ordinary skill in the art at the time of the invention would have had no idea that ACP-103 corresponds to the compound of Formula (I) or its pharmaceutically acceptable salt.

Andersson does not cure the defects of *Drug News 2001*. Andersson teaches a broad genus of compounds that encompasses the compound of Formula (I), however, the compound is not specifically disclosed in Andersson. The Examiner has not demonstrated how one of ordinary skill in the art would be motivated to select the specific variables from the genus of Andersson in order to arrive at the compound of the instant claims. As was the case in *Eisai* and *Takeda*, the prior art cited by the Examiner does not provide a "finite number of identified, predictable solutions," but a "broad selection of compounds any of which could have been selected as the lead compound for further investigation." *Takeda*, 429 F.3d at 1359; *Eisai*, 533 F.3d at 1357. Only with the benefit of hindsight could one of

[4] In *Takeda*, a post-*KSR* decision, the Federal Circuit also held that a structurally similar compound was not *prima facie* obvious because the prior art provide no motivation to make the specific change in structure. *Takeda Chemical Ind., Ltd. v. Alphapharm Pty., Ltd.*, 429 F.3d 1350 (Fed. Cir. 2007).

ordinary skill in the art reasonably be expected to arrive at the compound of the instant claims, and the use of hindsight is impermissible when evaluating the teaching of the prior art. *See In re McLaughlin*, 443 F.2d 1392, 1395 (C.C.P.A. 1972); *see also* MPEP § 2145, para. X.A. Simply put, there is no support for the change in structure from compounds of Andersson to the claimed compound of formula (I), therefore, a *prima facie* case of obvious cannot be made. *Eisai*, 533 F.3d at 1359; *Takeda*, 429 F.3d at 1356; *see also In re Baird,* 16 F.3d 380, 382, (Fed. Cir. 1994) (the mere fact that a species is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness); MPEP § 2144.08.

Moreover, the Examiner has not pointed to any specific compound in Andersson that could be selected by one of ordinary skill in the art as a "lead compound" that could be modified to arrive at the claimed compound. This type of teaching is necessary to support a *prima facie* case of structural obviousness. *See Eisai*, 533 F.3d at 1357; *Takeda*, 429 F.3d at 1356.

Goodman & Gilman's, which the Examiner cites only to allege that combinations of the compound of Formula (I) and second therapeutic agents are obvious, does not cure the defects of *Drug News 2001* and Andersson. (final Office Action, pages 4-5). Therefore, because none of the references cited by the Examiner disclose or suggest the compound of Formula (I) or a pharmaceutically acceptable salt thereof, claims 1-8 are not obvious over those references. Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

B. Applicants have demonstrated unexpected results that rebut even a *prima facie* case of obviousness.

As the Examiner is well aware, even a *prima facie* case of obviousness may be overcome with evidence of unexpected results. *In re May*, 574 F.2d 1082, 1094 (C.C.P.A. 1978); *In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987); *Ortho-McNeil Pharmaceutical v. Mylan Laboratories*, 348 F. Supp. 2d 713, 755 (N.D. W. Va. 2004); MPEP § 2145. Therefore, even assuming, *arguendo*, that the Examiner has stated a *prima facie* case of obviousness, Applicants submit that the compound and salts of the instant claims possess

unexpected properties sufficient to rebut a *prima facie* case of obviousness.[5] Submitted herewith is the declaration of Dr. Douglas W. Bonhaus ("Bonhaus Declaration"), which details experimental data showing that the compound of Formula I or pharmaceutically acceptable salts thereof possess unexpectedly superior biological properties as compared to the compounds of Andersson (*see, e.g.*, Bonhaus Declaration ¶¶ 19-20).

Specifically, Dr. Bonhaus provides data comparing about 100 compounds from Andersson with the tartrate and hydrochloride salts of the compound of Formula I (Bonhaus Declaration ¶¶ 8-10). As seen in the declaration, the compound of the claimed invention, or a pharmaceutically acceptable salt thereof were not only among the most potent 5-HT_{2A} receptor inverse agonists, but also had little or no undesired off-target activity, *i.e.*, demonstrated 5-HT_{2A} selectivity (Bonhaus Declaration ¶¶ 13-14). Finally, the compound of the claimed invention and its salts had high predicted oral bioavailability (Bonhaus Declaration ¶ 18). Considering these three attributes, the compound of Formula I and its salts are surprisingly superior as orally bioavailable selective 5-HT_{2A} receptor inverse agonists (Bonhaus Declaration ¶ 20).

In view of these unexpected results, the instant claims are not obvious. *In re May*, 574 F.2d at 1094. Therefore, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) be withdrawn.

[5] As shown above, Applicants do not concede that a *prima facie* case of obviousness has been legally established.

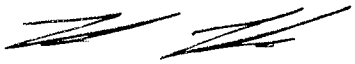
Conclusion

In view of the foregoing, the rejections of the claims should be withdrawn. Reconsideration, entry of the above remarks, and allowance of the pending claims are respectfully requested. If the Examiner believes it would be useful to advance prosecution, the Examiner is invited to telephone the undersigned at (858) 314-1200.

No fee is believed to be due with this submission. However, the Commissioner is hereby authorized to charge any required fee under 37 C.F.R. § 1.17, or any other required fee, or any credits, to Jones Day Deposit Account No. 503013 (referencing 598154-999016).

Respectfully submitted,

Date: October 14, 2008



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